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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

7590 07/28/2004

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EXAMINER	
SHARAREH, SHAHNAM J	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/218,660	UNGER ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 100,102,103,127,194-200,203,210-228,294-300,303,310-329,331-337,347-356 and 412.

DETAILED ACTION

Amendment filed on May 17, 2004 has been entered. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are pending.

Any rejection that is not addressed in this Office Action is obviated in view of the amendments.

Priority

1. The effective priority date used for the examination of the instant application is May 1, 1996.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 103 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 103 requires that the gas of claim 100 is derived at least in part from a gaseous precursor. Gaseous precursors encompass liquid substances such as perfluoropentane or perfluorohexane that are not in gaseous form at ambient conditions. (see for example instant specification at page 45, lines 25-32). However, claim 100 requires the gas-filled vesicle comprise an insoluble substance in gaseous form. Accordingly, claim 103 fails to further limit claim 100. Thus, the metes and bounds of the claim is not clear.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff US Patent 5,498,421 (Grinstaff) in view of Wallach US Patent 4,853,228, Allen US Patent 5,620,689, Glajch US Patent 5,147,631 and Quay US Patent 5,409,688.

The instant claims are directed toward a formulation comprising targeted phospholipid containing vesicles comprising a substantially insoluble perfluorocarbon substance which is in gaseous form at ambient conditions, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol. PVP, and copolymers thereof and wherein the vesicle is substantially free of crosslinked proteins and polymers. As defined by the instant specification at page 18, line 8-10, "substantially" refers to a measurement of greater than about 50%. Thus, such recitation is construed as the quantity and degree of cross-linking.

Grinstaff discloses a composition for in vivo delivery of a diagnostic or therapeutic agents comprising polymeric shell microbubbles (see col 7-8). Grinstaff teaches that the polymeric shell may be modified to include suitable agents, such as phospholipid (including Phosphotidylethnolamine "PE"). Grinstaff also states that various polymers such as polyalkylene and protein for targeting which may be

covalently bound to his shell, (see col 12, lines 14+). Microbubble structure of Grinstaff meet the limitations of the instant lipid vesicles.

Grinstaff specifically teaches the conjugation of a targeting moiety to polymeric shell to provide advantage of site-specific delivery of the diagnostic or therapeutic microbubbles (col 8-9). Grinstaff lacks explicit teaching of a linker that is attached to his polymeric shell via a covalent linkage.

Grinstaff at col 14, lines 28-35 also teaches the use of gases as its preferred ultrasound agents:

> Examples of diagnostic agents contemplated for use in the practice of the present invention include ultrasound contrast agents, radiocontrast agents (e.g., iodo-octanes, halocarbons, renografin, and the like), magnetic contrast agents (e.g., fluorocarbons, lipid soluble paramagnetic compounds, GdDTPA, aqueous paramagnetic compounds, and the like), as well as other agents (e.g., gases such as argon, nitrogen, carbon monoxide, carbon dioxide, helium, xenon, nitrous oxide, nitric oxide, nitrogen dioxide, and the like, as well as combinations of any two or more thereof).

However, Grinstaff does not enumerate any perfluorocarbon gases.

Wallace and Allen are used to show that covalent linkage between a lipid vesicle and a targeting ligand via a polymeric linker is conventional in the art. Wallace discloses a composition comprising lipid vesicles such as liposomes, which are used to the delivery of diagnostic or therapeutic agents, (see col 5, lines 8-20). Wallach also teaches that such lipid vesicles may be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity, (see col 4, lines 61+). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by

covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7).

Allen discloses a composition comprising lipid vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shell may be formed from a phospholipid such as PE, (see entire col 6-8). Attached to the vesicle shell is a polymer chain in which a ligand (antibody) is covalently bound thereto, (see col 5-6; fig. 1, col 12, lines 29-34). Wallace and Allen do not teach gas containing vesicles.

Glaijch and Quay are used to show that perfluorcarbon gases that are substantially insoluble at ambient temperature are expected to provide useful ultrasound contrast properties. For example, Glaijch enumerates the use of perfluoromethane (CF4) and perfluoroethane (C2F6) as effective as the gases such as O2, He, aragon etc. (see col 6, lines 57-65; col 13, lines 1-20).

It is noted that Grinstaff also enumerates O2, He, aragon as ultrasound contrast agents. Therefore, perfluoromethane or perfluoroethane of Glaijch are expected to be functionally equivalents to O2, He, Aragon.

Quay is used to show that perfluorocarbon gases such as perfluorobutane or perfluorpropane have effective ultrasound properties (see col 18, lines 15-35).

Since Grinstaff, Glaijch, Quay, Wallach and Allen all disclose compositions comprising targeted lipid-coated vesicles for in vivo delivery of a diagnostic or therapeutic agents, they are viewed to be in the same field of endeavor.

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the vesicle compositions of Grinstaff to include a targeting moiety via a linking group bound to the vesicle by a covalent linkage and further contain a perflurocarbon gas, because first Grinstaff suggests that a targeting moiety can be attached to the phospholipid walls of lipid vesicles, and as taught by Wallace and Allen a such targeting moieties can be covalently bound to the vesicle by a polymeric linking group. Further, Grinstaff encourages the use of art equivalent gaseous ultrasound agents, such as those enumerated in Glaich and Quay, in his compositions.

The ordinary skill in the art would have performed such modifications on Grinstaffs' vesicles because he would have had a reasonable expectation of success in improving the targeting, specificity, and stability of the lipid vesicle's activity in vivo.

Subsequently, as the instant methods require a mere in vivo application of the claimed compositions, it would have been obvious to one of ordinary skill in the art at the time of invention to administer such compositions in vivo for their preferred utility.

4. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace and Allen in view of Schneider US Patent 5,643,553 (Schneider) and Porter US Patent 5,648,098 (Porter).

5. Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive. Applicant argues that Schneider's microbubbles do not contain gas, rather, a liquid.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the rejection is based on the combined teachings of references and the combined teachings of the references meet all elements of the instant claims.

Contrary to Applicant's view, Schneider envisioned gaseous "microbubbles of air." (see col 1, lines 28-30). Further, Porter provides for various perflurocarbon gases such as perfluorobutane. Therefore, the combined teachings of the references provide for substituting Schneider's gas or even adding to Schneider's gas the perfluorobutane of Porter.

Applicant has also argued that Schneider teaches away from the instant claims because it distinguishes microcapsules from microbubbles. However, applicant has not provided any evidence substantiating the structural differences between the microbubbles of Schneider, as employed in the rejection, and the instant vesicles. Accordingly, the arguments are not found ~~percussive.~~ Persuasive

6. Claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff in view of Wallach, Allen, Glajich, Quay and further in view of Ginsburg US Patent 5,656,442 (Ginsburg).

The combination of Grinstaff, Wallach, Allen, Glaijch and Quay are described above. Such combination does not teach the specific targeting group of Arg-Gly-Asp ("RGD") or Lys-Gln-Ala-Gly-Asp-Val.

Ginsburg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55). Ginsburg further teaches that such amino-acid chains specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and that they can be used as a targeting ligand in an in vitro kit (abstract). Since Ginsburg teaches the same targeting agent encompassed in the instant claims, it also provides for the binding affinity of the targeting ligand.

Although the combination of the teachings of Grinstaff, Wallach, Allen, Glaijch and Quay do not specifically recite the use of Lys-Gln-Ala-Gly-Asp-Val or RGD as a targeting agent, they suggest the use of any suitable targeting agent to improve specificity of their drug delivery system. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use a suitable targeting agent such as those taught by Ginsburg specific for tissue thrombosis and thrombotic sites, because the ordinary artisan would have had a reasonable expectation of success to improve specificity of a drug delivery vesicles to platelet membranes when employing Ginsburgs' targeting agents.

7. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach and Allen in view of Schneider and Porter and further in view of Ginsburg.

8. Applicant's arguments towards this rejection have been considered but are not found persuasive for the similar reason as described in para. 5 above. Aaccordingly, the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action, because it has narrowed the scope of the ending claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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RUSSELL TRAVERS
PRIMARY EXAMINER